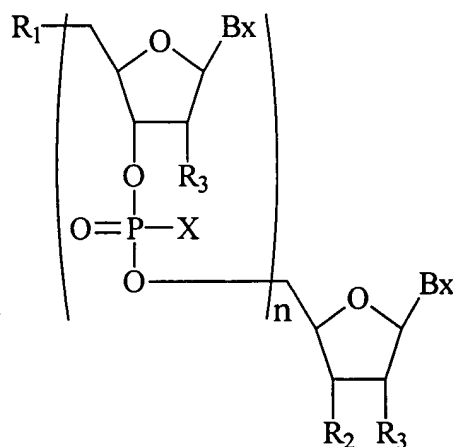


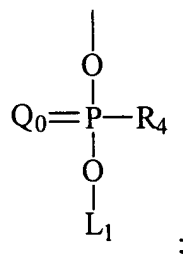
What is claimed is:

1. A process for preparing an oligonucleotide having the formula:



wherein:

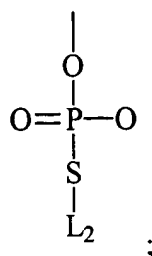
R_1 is hydroxyl, a protected hydroxyl or a group having the formula:



Q_0 is O or S;

R_4 is O^- , hydroxyl or a protected hydroxyl;

R_2 is hydroxyl, a protected hydroxyl or a group having the formula:



each R_3 is H, a 2'-substituent group or a protected 2'-substituent group;

each X is, independently, O⁻, hydroxyl, protected hydroxyl or -S-L₃;

each Bx is an optionally protected heterocyclic base moiety;

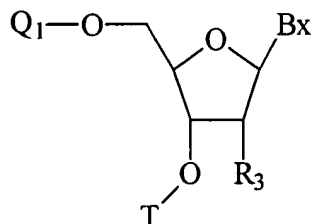
n is from 3 to about 50; and

L₁, L₂ and each of said L₃ are, independently, a conjugate group;

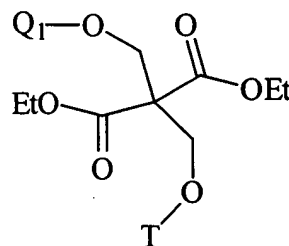
wherein at least two of said X or at least one of said X and one of said R₂ comprise a conjugate group;

comprising the steps of:

a) providing a derivatized solid support for oligonucleotide synthesis, said derivatized solid support being derivatized with a group having one of the structures:



or



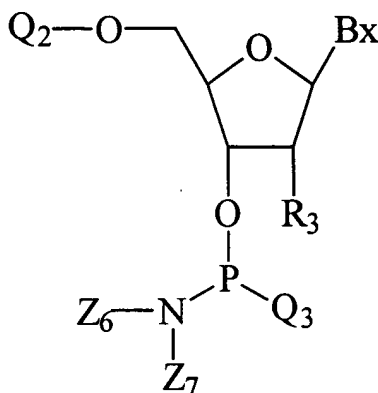
wherein

T is a bifunctional linking moiety linked to the solid support; and

Q₁ is an acid labile hydroxyl protecting group;

b) treating said derivatized solid support with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group;

c) reacting said free hydroxyl group with a phosphoramidite composition to form an extended compound, said phosphoramidite composition having the formula:



wherein

Q₂ is a 5'-terminal acid labile hydroxyl protecting group;

Q₃ is a phosphorus protecting group; and

Z₆ and Z₇ are, independently, C₁₋₆ alkyl;

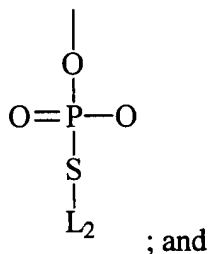
or Z₆ and Z₇ are joined together to form a 4- to 7-membered heterocyclic ring system including the nitrogen atom to which Z₆ and Z₇ are attached, wherein said ring system optionally includes at least one additional heteroatom selected from O, N and S;

d) oxidizing said extended compound to form an oxidized compound, or treating said extended compound with an acidic reagent to deblock said 5'-terminal acid labile hydroxyl protecting group of said extended compound to give a free hydroxyl group and repeating step c) at least one time followed by oxidizing said extended compound to form an oxidized compound;

e) treating said oxidized compound with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group and repeating steps c) and d) at least three times to form an extended oxidized compound;

- f) treating said extended oxidized compound for a time and under conditions effective to remove at least one phosphorus protecting group giving at least one deblocked phosphorothioate linkage;
- g) reacting said deblocked phosphorothioate linkage with a conjugate group that is reactive with and forms a covalent bond with said deblocked phosphorothioate linkage; and
- h) repeating steps f) and g) to give said oligonucleotide.

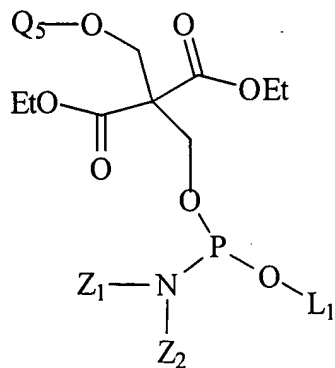
2. The process of Claim 1 wherein R_2 is a group having the formula:



at least one of said X is $-S-L_3$.

- 3. The process of Claim 2 wherein L_2 is different from at least one of said L_3 .
- 4. The process of Claim 1 wherein at least two of said X are independently $-S-L_3$.
- 5. The process of Claim 4 wherein at least one of said L_3 is different from at least one other of said L_3 .
- 6. The process of Claim 1 wherein each of said L_1 , L_2 and L_3 is independently selected from the group consisting of intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers.

7. The process of Claim 6 wherein each of said L_1 , L_2 and L_3 is independently selected from the group consisting of cholesterol, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.
8. The process of Claim 1 wherein each of said Q_3 is individually selected from the group consisting of cyanoethyl, diphenylsilylethyl, cyanobutenyl, cyano *p*-xylyl (CPX), methyl-N-trifluoroacetyl ethyl (META) and acetoxo phenoxy ethyl (APOE) groups.
9. The process of Claim 1 wherein R_1 is a protected hydroxyl group and further comprising the steps of treating said oligonucleotide with a reagent effective to deblock said protected hydroxyl group to give a free hydroxyl group and reacting said free hydroxyl group with a compound of the formula:



to form a 5'-functionalized compound;

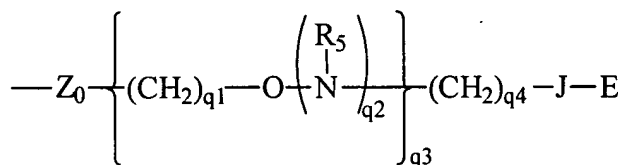
wherein Q_5 is an acid labile hydroxyl protecting group.

10. The process of Claim 9 further comprising the step of treating said 5'-functionalized compound with a capping agent to form a capped compound.

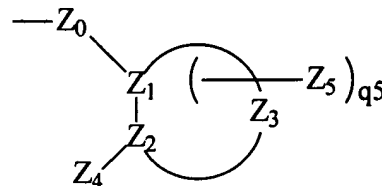
11. The process of Claim 9 further comprising treating said oligonucleotide with a reagent effective to remove said acid labile hydroxyl protecting group.
12. The process of Claim 11 further comprising treating said oligonucleotide with a basic reagent.
13. The process of Claim 12 wherein said basic reagent is aqueous piperidine.
14. The process of Claim 1 wherein n is from about 8 to about 30.
15. The process of Claim 14 wherein n is from about 15 to about 25.
16. The process of Claim 1 wherein each of said Q₁ and Q₂ is independently selected from the group consisting of trimethoxytrityl, dimethoxytrityl (DMT), monomethoxytrityl, 9-phenyl-xanthen-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthen-9-yl (Mox).
17. The process of Claim 1 wherein each of said Bx is independently selected from the group consisting of adenine, guanine, thymine, cytosine, uracil, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, 5-halocytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-substituted adenines and guanines, 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine and 3-deazaadenine.
18. The process of Claim 1 wherein at least one of said L₁, L₂, and L₃ is attached to the oligonucleotide through a linking group.

19. The process of Claim 18 wherein the linking group comprises a dialkylglycerol linker.
20. The process of Claim 1 wherein each of said Z_6 and Z_7 is isopropyl.
21. The process of Claim 1 wherein each R_3 is, independently, C_1 - C_{20} alkyl, C_2 - C_{20} alkenyl, C_2 - C_{20} alkynyl, C_5 - C_{20} aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

or each substituent group has one of formula I or II:



I



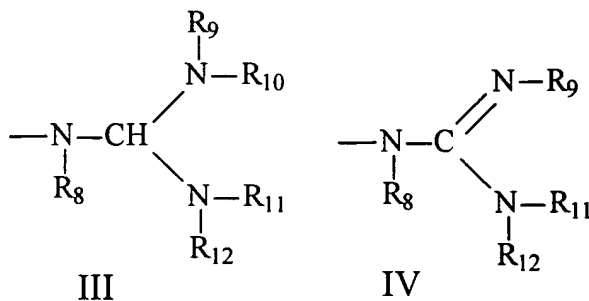
II

wherein:

Z_0 is O, S or NH;

J is a single bond, O or C(=O);

E is C_1 - C_{10} alkyl, $N(R_5)(R_6)$, $N(R_5)(R_7)$, $N=C(R_5)(R_6)$, $N=C(R_5)(R_7)$ or has one of formula III or IV;



each R_8 , R_9 , R_{10} , R_{11} and R_{12} is, independently, hydrogen, $C(O)R_{13}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R_9 and R_{10} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R_{11} and R_{12} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{13} is, independently, substituted or unsubstituted C_1 - C_{10} alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

R_5 is T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R_5 and R_6 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, wherein said substitution is OR_3 , SR_3 , NH_3^+ , $N(R_{14})(R_{15})$, guanidino or acyl where said acyl is an acid amide or an ester;

or R_5 and R_6 , together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R_{21} , T and L, together, are a chemical functional group;

each R_{14} and R_{15} is, independently, H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{14} and R_{15} , together, are a nitrogen protecting group;

or R_{14} and R_{15} are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)R_{16}$, $C(=O)N(H)R_{16}$ or $OC(=O)N(H)R_{16}$;

R_{16} is H or C_1 - C_8 alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms wherein said heteroatoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(R_5)(R_6)$ OR₅, halo, SR₅ or CN;

each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

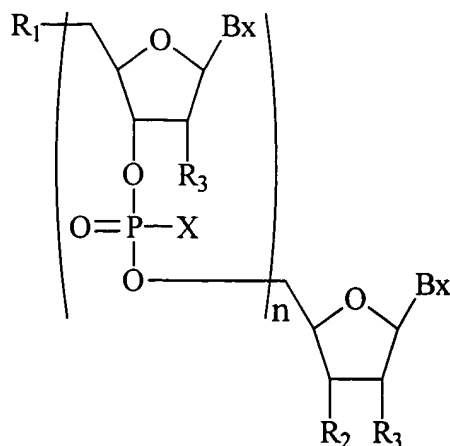
q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

q_5 is from 0, 1 or 2; and

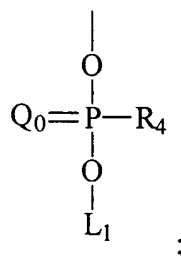
provided that when q_3 is 0, q_4 is greater than 1.

22. A process for preparing an oligonucleotide having the formula:



wherein:

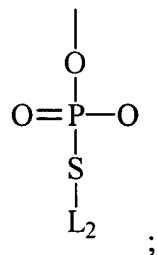
R_1 is a group having the formula:



Q_0 is O or S;

R_4 is O⁻, hydroxyl, or a protected hydroxyl;

R_2 is hydroxyl, a protected hydroxyl or a group having the formula:



each R_3 is H, a 2'-substituent group or a protected 2'-substituent group;

each X is, independently, O⁻, hydroxyl, protected hydroxyl, or -S- L_3 ;

each Bx is an optionally protected heterocyclic base moiety;

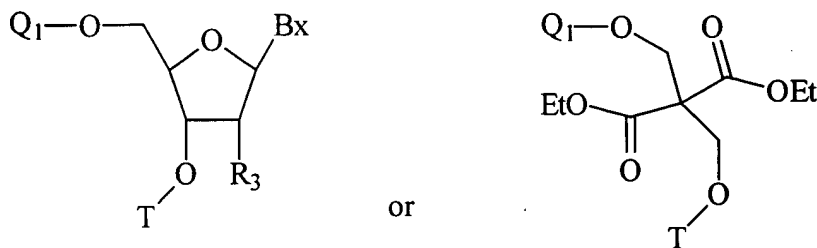
n is from 3 to about 50; and

L_1 , L_2 and each of said L_3 are, independently, a conjugate group;

wherein said R_1 and at least one of said R_2 or said X comprise a conjugate group;

comprising the steps of:

- a) providing a derivatized solid support for oligonucleotide synthesis, said derivatized solid support being derivatized with a group having one of the structures:

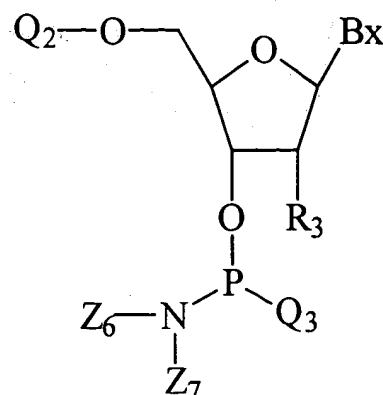


wherein

T is a bifunctional linking moiety linked to the solid support; and

Q_1 is an acid labile hydroxyl protecting group;

- b) treating said derivatized solid support with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group;
- c) reacting said free hydroxyl group with a phosphoramidite composition to form an extended compound, said phosphoramidite composition having the formula:



wherein

Q_2 is a 5'-terminal acid labile hydroxyl protecting group;

Q_3 is a phosphorus protecting group; and

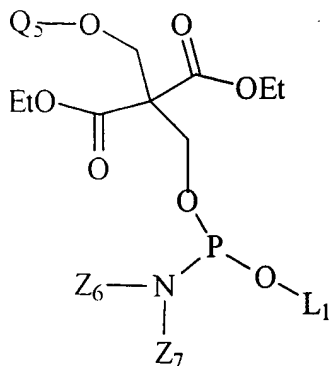
Z_6 and Z_7 are, independently, C_{1-6} alkyl;

or Z_6 and Z_7 are joined together to form a 4- to 7-membered heterocyclic ring system including the nitrogen atom to which Z_6 and Z_7 are attached, wherein said ring system optionally includes at least one additional heteroatom selected from O, N and S;

d) oxidizing said extended compound to form an oxidized compound, or treating said extended compound with an acidic reagent to deblock said 5'-terminal acid labile hydroxyl protecting group of said extended compound to give a free hydroxyl group and repeating step c) at least one time followed by oxidizing said extended compound to form an oxidized compound;

e) treating said oxidized compound with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group and repeating steps c) and d) at least three times to form an extended oxidized compound;

f) treating said extended oxidized compound with a reagent effective to deblock said protected hydroxyl group to give a free hydroxyl group and reacting said free hydroxyl group with a compound of formula:



thereby forming a 5'-functionalized compound;

wherein

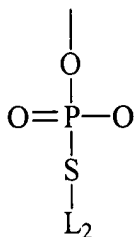
Q_5 is an acid labile hydroxyl protecting group;

g) treating said 5'-functionalized compound for a time and under conditions effective to remove at least one phosphorus protecting group giving at least one deblocked phosphorothioate linkage; and

h) reacting said deblocked phosphorothioate linkage with a conjugate group that is reactive with and forms a covalent bond with said deblocked phosphorothioate linkage to give said oligonucleotide.

23. The process of Claim 22 further comprising the step of treating said 5'-functionalized compound with a capping agent to form a capped compound.

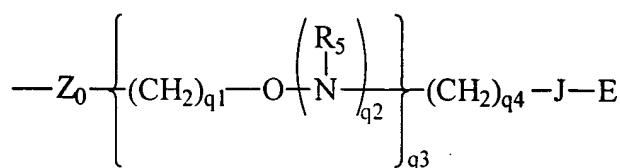
24. The process of Claim 22 wherein said R_2 is a group having the formula:



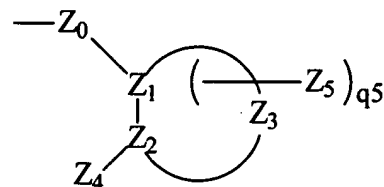
25. The process of Claim 24 wherein L_1 is different from L_2 .
26. The process of Claim 22 wherein at least one of said X is -S- L_3 .
27. The process of Claim 26 wherein L_1 is different from L_3 .
28. The process of Claim 22 wherein each of said L_1 , L_2 and L_3 is independently selected from the group consisting of intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers.
29. The process of Claim 28 wherein each of said L_1 , L_2 and L_3 is independently selected from the group consisting of cholesterol, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.
30. The process of Claim 1 wherein each of said Q_3 is independently selected from the group consisting of cyanoethyl, diphenylsilylethyl, cyanobutenyl, cyano *p*-xylyl (CPX), methyl-N-trifluoroacetyl ethyl (META) and acetoxymethoxy ethyl (APOE) groups.
31. The process of Claim 22 wherein said 5'-functionalized compound is treated in step g) to remove all phosphorus protecting groups.
32. The process of Claim 22 wherein n is from about 8 to about 30.
33. The process of Claim 32 wherein n is from about 15 to about 25.

34. The process of Claim 22 wherein each of said Q₁ and Q₂ is independently selected from the group consisting of trimethoxytrityl, dimethoxytrityl (DMT), monomethoxytrityl, 9-phenyl-xanthen-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthen-9-yl (Mox).
35. The process of Claim 22 wherein each of said Bx is independently selected from the group consisting of adenine, guanine, thymine, cytosine, uracil, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, 5-halocytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-substituted adenines and guanines, 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine and 3-deazaadenine.
36. The process of Claim 22 wherein at least one of said L₁, L₂, and L₃ is attached to the oligonucleotide through a linking group.
37. The process of Claim 36 wherein the linking group comprises a dialkylglycerol linker.
38. The process of Claim 22 wherein each of said Z₆ and Z₇ is isopropyl.
39. The process of Claim 22 wherein each R₃ is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-alkenyl, O-alkynyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol, S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

or each substituent group has one of formula I or II:



I



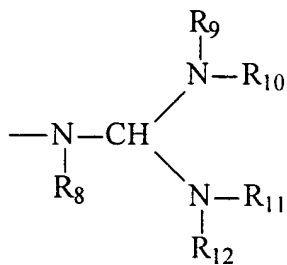
II

wherein:

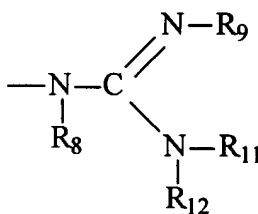
Z_0 is O, S or NH;

J is a single bond, O or C(=O);

E is C_1 - C_{10} alkyl, $N(R_5)(R_6)$, $N(R_5)(R_7)$, $N=C(R_5)(R_6)$, $N=C(R_5)(R_7)$ or has one of formula III or IV;



III



IV

each R_8 , R_9 , R_{10} , R_{11} and R_{12} is, independently, hydrogen, $C(O)R_{13}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy, carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R_9 and R_{10} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R_{11} and R_{12} , together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R_{13} is, independently, substituted or unsubstituted C_1 - C_{10} alkyl, trifluoromethyl, cyanoethoxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)-ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

R_5 is T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R_5 and R_6 is, independently, H, a nitrogen protecting group, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, wherein said substitution is OR_3 , SR_3 , NH_3^+ , $N(R_{14})(R_{15})$, guanidino or acyl where said acyl is an acid amide or an ester;

or R_5 and R_6 , together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R_{21} , T and L, together, are a chemical functional group;

each R_{14} and R_{15} is, independently, H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_{14} and R_{15} , together, are a nitrogen protecting group;

or R_{14} and R_{15} are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)R_{16}$, $C(=O)N(H)R_{16}$ or $OC(=O)N(H)R_{16}$;

R_{16} is H or C_1 - C_8 alkyl;

Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 heteroatoms wherein said heteroatoms

are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(R_5)(R_6)OR_5$, halo, SR_5 or CN ;

each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

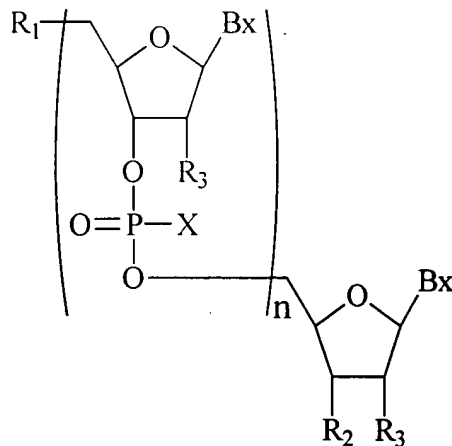
q_3 is 0 or an integer from 1 to 10;

q_4 is an integer from 1 to 10;

q_5 is from 0, 1 or 2; and

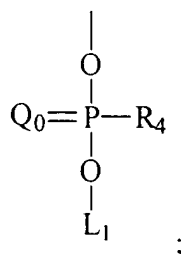
provided that when q_3 is 0, q_4 is greater than 1.

40. A process for preparing an oligonucleotide having the formula:



wherein:

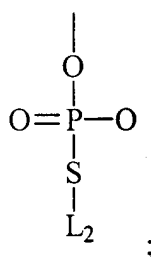
R_1 is hydroxyl, a protected hydroxyl or a group having the formula:



Q_0 is O or S;

R_4 is O^- , a hydroxyl, or a protected hydroxyl;

R_2 is a group having the formula:



each R_3 is H, a 2'-substituent group or a protected 2'-substituent group;

each X is, independently, O^- , hydroxyl, protected hydroxyl, or $-\text{S}-\text{L}_3$;

each Bx is an optionally protected heterocyclic base moiety;

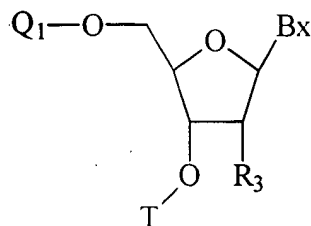
n is from 3 to about 50; and

L_1 , L_2 and each of said L_3 are, independently, a conjugate group;

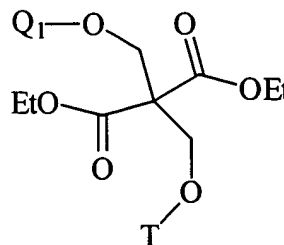
comprising the steps of:

a) providing a derivatized solid support for oligonucleotide synthesis, said

derivatized solid support being derivatized with a group having one of the structures:



or



step c) at least one time followed by oxidizing said extended compound to form an oxidized compound;

e) treating said oxidized compound with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group and repeating steps c) and d) at least three times to form an extended oxidized compound;

f) treating said further extended compound for a time and under conditions effective to remove a 3'-terminal phosphorus protecting group giving a 3'-terminal deblocked phosphorothioate linkage; and

g) reacting said deblocked phosphorothioate linkage with a conjugate group that is reactive with and forms a covalent bond with said deblocked phosphorothioate linkage.

41. The process of Claim 40 wherein at least one of L_1 , L_2 , and L_3 is attached to the oligonucleotide through a linking group.

42. The process of Claim 41 wherein the linking group comprises a dialkylglycerol linker.

43. The process of Claim 40 wherein each of said Z_1 and Z_2 is isopropyl.

44. The process of Claim 40 wherein each of said L_1 , L_2 and L_3 is independently selected from the group consisting of intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers.

45. The process of Claim 44 wherein each of said L_1 , L_2 and L_3 is independently selected from the group consisting of cholesterol, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.

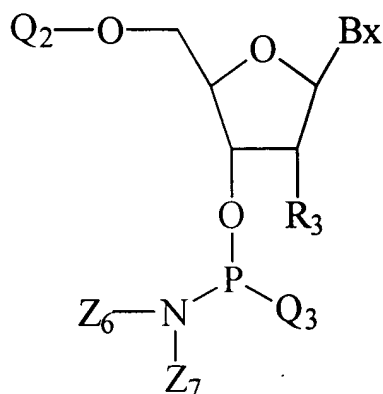
wherein

T is a bifunctional linking moiety linked to the solid support; and

Q₁ is an acid labile hydroxyl protecting group;

b) treating said derivatized solid support with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group;

c) reacting said free hydroxyl group with a phosphoramidite composition to form an extended compound, said phosphoramidite composition having the formula:



wherein

Q₂ is a 5'-terminal acid labile hydroxyl protecting group;

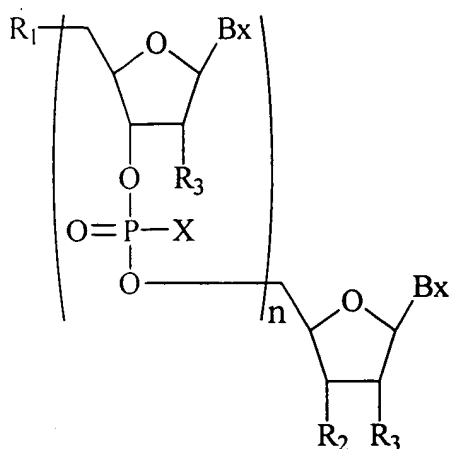
Q₃ is a phosphorus protecting group; and

Z₆ and Z₇ are, independently, C₁₋₆ alkyl;

or Z₆ and Z₇ are joined together to form a 4- to 7-membered heterocyclic ring system including the nitrogen atom to which Z₆ and Z₇ are attached, wherein said ring system optionally includes at least one additional heteroatom selected from O, N and S;

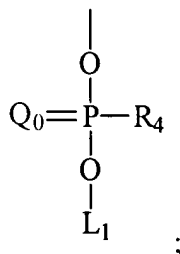
d) oxidizing said extended compound to form an oxidized compound, or treating said extended compound with an acidic reagent to deblock said 5'-terminal acid labile hydroxyl protecting group of said extended compound to give a free hydroxyl group and repeating

46. The process of Claim 40 wherein L_2 is different from L_1 and L_3 .
47. The process of Claim 40 wherein each of said Q_3 is independently selected from the group consisting of cyanoethyl, diphenylsilylethyl, cyanobutenyl, cyano *p*-xylyl (CPX), methyl-N-trifluoroacetyl ethyl (META) and acetoxo phenoxy ethyl (APOE) groups.
48. The process of Claim 40 wherein each of said Q_1 and Q_2 is independently selected from the group consisting of trimethoxytrityl, dimethoxytrityl (DMT), monomethoxytrityl, 9-phenyl-xanthen-9-yl (Pixyl) and 9-(*p*-methoxyphenyl)xanthen-9-yl (Mox).
49. The process of Claim 40 wherein each Bx is independently selected from the group consisting of adenine, guanine, thymine, cytosine, uracil, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, 5-halocytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-substituted adenines and guanines, 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine and 3-deazaadenine.
50. A process for preparing an oligonucleotide having the formula:



wherein:

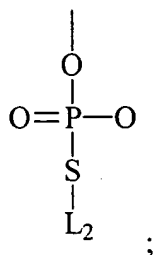
R_1 is a group having the formula:



Q_0 is O or S;

R_4 is O⁻, hydroxyl, or a protected hydroxyl;

R_2 is hydroxyl, a protected hydroxyl or a group having the formula:



each R_3 is H, a 2'-substituent group or a protected 2'-substituent group;

each X is, independently, O⁻, hydroxyl, a protected hydroxyl, or -S- L_3 ;

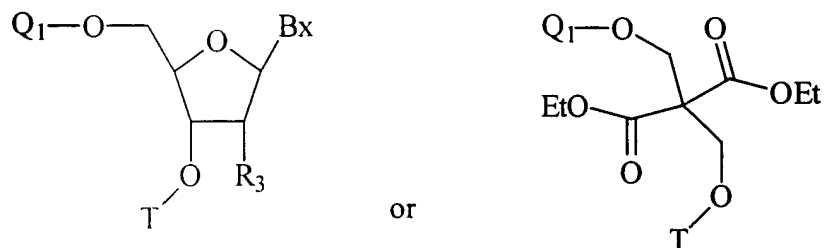
each Bx is an optionally protected heterocyclic base moiety;

n is from 3 to about 50; and

L_1 , L_2 and each of said L_3 are, independently, a conjugate group;

comprising the steps of:

- a) providing a derivatized solid support for oligonucleotide synthesis, said derivatized solid support being derivatized with a group having one of the structures:

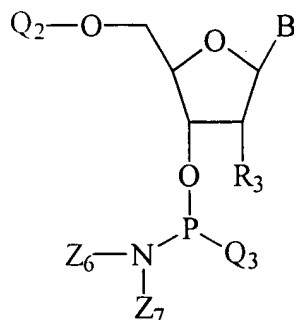


wherein

T is a bifunctional linking moiety linked to the solid support; and

Q_1 is an acid labile hydroxyl protecting group;

- b) treating said derivatized solid support with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group;
- c) reacting said free hydroxyl group with a phosphoramidite composition to form an extended compound, said phosphoramidite composition having the formula:



wherein

Q_2 is a 5'-terminal acid labile hydroxyl protecting group;

Q_3 is a phosphorus protecting group; and

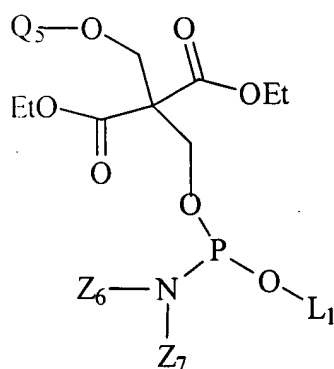
Z_6 and Z_7 are, independently, C_{1-6} alkyl;

or Z_6 and Z_7 are joined together to form a 4- to 7-membered heterocyclic ring system including the nitrogen atom to which Z_6 and Z_7 are attached, wherein said ring system optionally includes at least one additional heteroatom selected from O, N and S;

d) oxidizing said extended compound to form an oxidized compound, or treating said extended compound with an acidic reagent to deblock said 5'-terminal acid labile hydroxyl protecting group of said extended compound to give a free hydroxyl group and repeating step c) at least one time followed by oxidizing said extended compound to form an oxidized compound;

e) treating said oxidized compound with an acidic reagent to deblock said acid labile hydroxyl protecting group to give a free hydroxyl group and repeating steps c) and d) at least three times to form an extended oxidized compound;

f) treating said extended oxidized compound with an acidic reagent effective to deblock said 5'-terminal acid labile hydroxyl protecting group to give a free hydroxyl group and reacting said free hydroxyl group with a compound of the formula:



thereby forming a 5'-functionalized compound;

wherein

Q₃ is an acid labile hydroxyl protecting group;

51. The process of Claim 50 further comprising the step of treating said 5'-functionalized compound with a capping agent to form a capped compound.
52. The process of Claim 50 wherein at least one of said L₁, L₂, and L₃ is attached to the oligonucleotide through a linking group.
53. The process of Claim 52 wherein the linking group comprises a dialkylglycerol linker.
54. The process of Claim 50 wherein each of said Z₆ and Z₇ is isopropyl.
55. The process of Claim 50 wherein each of said L₁, L₂ and L₃ is independently selected from the group consisting of intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers.
56. The process of Claim 55 wherein each of said L₁, L₂ and L₃ is independently selected from the group consisting of cholesterol, phospholipids, biotin, phenazine, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes.
57. The process of Claim 50 wherein L₁ is different from L₂ and L₃.
58. The process of Claim 50 wherein each of said Q₃ is independently selected from the group consisting of cyanoethyl, diphenylsilylethyl, cyanobutenyl, cyano *p*-xylyl (CPX), methyl-N-trifluoroacetyl ethyl (META) and acetoxo phenoxy ethyl (APOE) groups.

59. The process of Claim 50 wherein each of said Q_1 and Q_2 is independently selected from the group consisting of trimethoxytrityl, dimethoxytrityl (DMT), monomethoxytrityl, 9-phenyl-xanthen-9-yl (Pixyl) and 9-(p-methoxyphenyl)xanthen-9-yl (Mox).
60. The process of Claim 50 wherein each of said Bx is independently selected from the group consisting of adenine, guanine, thymine, cytosine, uracil, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine, 2-thiocytosine, 5-halouracil, 5-halocytosine, 5-propynyl uracil, 5-propynyl cytosine, 6-azo uracil, 6-azo cytosine, 6-azo thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-substituted adenines and guanines, 5-substituted uracils and cytosines, 7-methylguanine, 7-methyladenine, 8-azaguanine, 8-azaadenine, 7-deazaguanine, 7-deazaadenine, 3-deazaguanine and 3-deazaadenine.